Activation of the IL-1 Gene in UV-Irradiated Mouse Skin: Association with Inflammatory Sequelae and Pharmacologic Intervention

Don E. Griswold, Janice R. Connor, Barbara J. Dalton, John C. Lee, Philip Simon, Leonard Hillegass, David J. Sieg, and Nabil Hanna

Inflammation Section, Division of Pharmacological Sciences (DEG, LH, DJS); and Department of Cell Sciences (JRC, BJD, JCL), SmithKline Beecham Pharmaceuticals, Research and Development, King of Prussia, Pennsylvania, U.S.A.

The relationship between ultraviolet irradiation, interleukin-1 production, and inflammatory sequelae and the pharmacologic inhibition of these events was investigated in Balb/c mice exposed to ultraviolet irradiation from a bank of six Westinghouse FS40 sunlamps. The resulting edema (66% increase), inflammatory cell infiltration, and rise in the acute-phase reactant (fourfold) serum amyloid P component was preceded by the activation of the interleukin-1 beta gene and enhanced product formation. Administration of dexamethasone, which is known to inhibit interleukin-1 production, inhibited the inflammatory response to ultraviolet irradiation. Thus, production of interleukin-1 may be one of the initial events leading to the consequences of ultraviolet irradiation exposure. *J Invest Dermatol 97:1019–1023, 1991*

The reduction of stratospheric ozone over the past 17 years has raised concern over the possibility that further erosion will increase exposure to ultraviolet (UV) irradiation [1,2]. UV-irradiant energy has been shown to produce marked pathophysiologic responses that range from sunburn to skin cancer [3,4] and the systemic consequences of UV irradiation include leukocytosis and fever, which most likely result from the release of cytokines including interleukin-1 (IL-1) [4,5]. The production of IL-1–like biologic activity [epidermal cell thymocyte-activating factor (ETAF)] from UV-irradiated skin [6,7] and keratinocytes, in vitro [8], has been shown. Furthermore, activation of IL-1 gene expression has been shown in cultured human keratinocyte [9]. The current model was devised to address the temporal sequence of local and systemic responses following UV irradiation. In addition, it was hoped that such a model would be useful for the pharmacologic evaluation of compounds that inhibit the production of IL-1.

Using UV-induced dermal inflammation in Balb/c mice, it was possible to determine the temporal relationship between the pathophysiologic events and the activation of the IL-1 beta gene. Furthermore, the inflammatory sequelae were inhibited by the administration of dexamethasone, a drug known to inhibit IL-1 production [10].

Manuscript received February 13, 1991; accepted for publication July 19, 1991.

Dr. Simon's current address: Ciba-Geigy Pharmaceuticals, 556 Morris Ave., Summit, New Jersey 07901.

Dr. Hanna's current address: IDEC Pharmaceuticals Corp. 11099 N. Torrey Rd. Ste. 160, LaJolla, California 92037.

Manuscript received February 13, 1991; accepted for publication July 19, 1991.

Reprint requests to: Dr. D.E. Griswold, Inflammation Section, Division of Pharmacological Sciences, SmithKline Beecham Pharmaceuticals, Research and Development, P.O. Box 1539, King of Prussia, PA 19406.

Abbreviations:

BSA: bovine serum albumin
CO_2: carbon dioxide
dCTP: cytidine triphosphate
EL-4/IL-2: EL4/interleukin-2
ETAF: epidermal cell thymocyte-activating factor
HTAB: hexadecyltrimethylammonium bromide
IL-1: interleukin-1
MPO: myeloperoxidase
ODI: o-dianisidine
oligo-dT: oligomeric thymidine
RNA: ribonucleic acid
RPMI: Roswell Park Medical Institute
SAP: serum amyloid P component
SDS: sodium dodecyl sulfate
SSC: sodium chloride, sodium citrate
TNF: tumor necrosis factor
UV: ultraviolet

MATERIALS AND METHODS

Animals Balb/c male mice (Charles River Laboratories, Portage, NC) were maintained in a barrier-sustained facility. The weight of the mice used range from 19 to 25 g.

Assay of Ear Swelling Ear thickness was quantified as previously described [11] using a constant pressure thickness gauge (Mitutoyo, Japan). The ear thickness was expressed as mean ear thickness $\pm$ SEM $\times 10^{-3}$ cm.

UV Irradiation and Sampling Where appropriate, the backs of mice were shaved the day prior to irradiation. Animals were then exposed to a bank of six FS40 Westinghouse UV lamps. The output and characteristics of these lamps have been well described, most recently by Kim, Kripke, and Ullrich [12]. Briefly, these lamps emit a spectrum of wavelengths from 270 to 320 nm with 65% emission within the UVB range (280–320 nm). The radiant energy was monitored using a UVX radiometer (American Ultraviolet, Chatham, NJ). The radiant energy output at the level the animals were irradiated was $1261.33 \pm 36.02 \mu W/cm^2$ or $1.26 mJ/cm^2$/second. The animals were housed in plastic cages without lids and exposed to the lights for the time periods indicated. Blood was collected to provide serum for assay of serum amyloid P component (SAP). Skin biopsies were performed in a sterile environment and sterility was maintained for subsequent experiments.

0022-202X/91/$03.50

Table I. Dose Response of UV Irradiation on Mouse Ear Swelling and SAP Response[a]

UV Irradiation (hours)	Ear Thickness ($\times 10^3$ cm)	SAP Concentration (μg/ml)
None	24.4 ± 0.9	33.7 ± 3.5
0.5	40.4 ± 4.6	130.2 ± 5.4
1.0	44.8 ± 5.4	154.9 ± 4.4
2.0	58.4 ± 5.8	164.5 ± 10.9
3.0	59.8 ± 2.4	198.0 ± 14.6

[a] Balb/c mice (n = 5/group) were exposed to UV irradiation for the time interval indicated. Forty-eight hours later, ear swelling was determined using a constant pressure thickness gauge and serum was obtained and assayed by quantitative Western blot for SAP concentration. All values are the mean ±SEM of 5 animals/group. All differences were found to be statistically different from the appropriate control at a $p < 0.01$ or better.

Explant Culture for IL-1 At the time periods indicated, two 10-mm biopsies were obtained aseptically from each mouse following CO_2 asphyxiation. The biopsies were placed into RPMI 1640 containing 5% endotoxin-free fetal calf serum with gentamicin and incubated in a 5% CO_2 atmosphere at 37°C. Tissue culture fluids were harvested either 3 or 24 h later and assayed for IL-1 biologic activity by the EL-4/IL-2 production assay as previously described [13].

Assay for SAP The assay for SAP was accomplished using a quantitative Western blot analysis as previously described by this laboratory [14].

Myeloperoxidase Assay The method of Bradley et al [15] was used to quantify myeloperoxidase activity. Ice-cold, minced tissues were homogenized (10% w/v) in 0.05 M phosphate buffer (pH = 6.0) containing 5 mg/ml, hexadecyltrimethylammonium bromide (HTAB) (Sigma Chemical Co., St. Louis, MO) using a tissumizer (Tekmar Co., Cincinnati, OH) to extract the enzyme. The appearance of a colored product from the myeloperoxidase (MPO)-dependent reaction of o-dianisidine (ODI) (0.167 mg/ml, Sigma Chemical Co.) and hydrogen peroxide (0.0005%, Sigma Chemical Co.) in 0.05 M phosphate buffer (pH 6.0) was measured spectrophotometrically at 460 nm. Supernatant MPO activity was quantified kinetically (change in absorbance over 3 min sampled at 15-second intervals) using a Beckman DU-7 spectrophotometer with Kinetics Analysis (Beckman Instruments, Inc.). One unit of MPO activity is defined as that degrading 1 μM of peroxide per minute at 25°C.

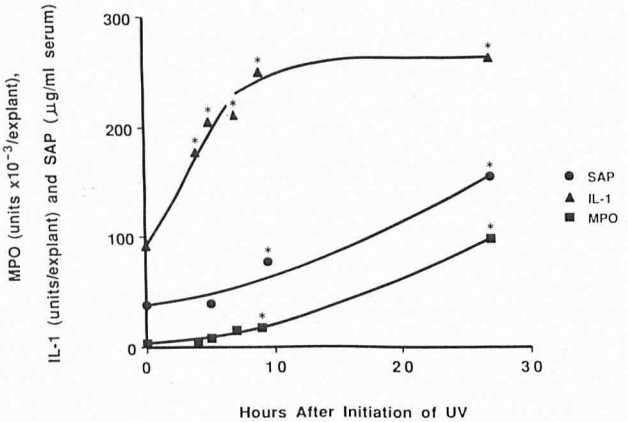

Figure 1. Time course of production of IL-1, serum amyloid P component (SAP), and myeloperoxidase (MPO) after UV irradiation. The backs of Balb/c male mice were shaved the day prior to irradiation. Animals were exposed to a bank of six FS40 Westinghouse UV lamps. The radiant energy output at the level of the animals was 1261.33 ± 36.02 μW/cm². They were exposed to the lights for 3 h. Blood was collected either from cardiac puncture or tail vein for assay of SAP. Skin biopsies were taken for explant culture for IL-1 and MPO assay. The biopsies were placed into RPMI 1640 containing 5% endotoxin-free fetal calf serum with gentamicin. Tissue culture fluids were harvested 24 h later and assayed for IL-1 biologic activity. Myeloperoxidase activity of additional biopsies was assayed using the method of Bradley et al [15]. An *asterisk* indicates that the data are statistically significant from unirradiated control values.

Extraction of RNA and Northern Blot Analysis To extract ribonucleic acid (RNA), skins were frozen in liquid nitrogen immediately upon harvest, then pulverized with a mortar and pestle, and homogenized in 4 M guanidinium thiocyanate (Fluka, Rolonkoma, NY) with the aid of a tissumizer, and the extracts were centrifuged through CsCl and total RNA isolated by the method of McCandliss et al [16]. As a positive control for cross-species hybridization of the human IL-1 alpha cDNA probe to the murine RNA, a murine macrophage cell line, P388D1, was prepared. The cells were cultured in the presence of mezerine (10^{-8} M) and cycloheximide (10 μg/ml, Sigma Chemical Co., St. Louis, MO) for 5 h. Polyadenylated RNA from these cells was used for Northern analysis. Polyadenylated RNA was prepared using oligomeric thymidine (oligo-dT) (Collaborative Research, Inc., Lexington, MA) chromatography [17]. For Northern blots, RNA was fractionated on 1.5% agarose gels containing formaldehyde (Fluka, Rokonkoma, NY) and transferred to nitrocellulose (Schleicher and Schuell, Keene, NH). An RNA ladder (Bethesda Research Laboratories, Gaithersburg, MD) was run adjacent to the samples as a size marker. Blots were pre-hybridized for 6–18 h at 42°C in 50% formamide, 5 × sodium chloride, sodium citrate (SSC) (20 × SSC: 3 M sodium chloride, 0.3 M sodium citrate), 5 × Denhardt's (100 × Denhardt's: 2% each of polyvinyl pyrrolidone-40, Ficoll 400, BSA fraction V), 25 mM sodium phosphate and 250 mg/ml heat-denatured, sheared salmon sperm DNA and hybridized for 16–20 h at 42°C in a similar solution containing 1 × Denhardt's and 10% dextran sulfate [18]. cDNA probes were labeled with (alpha-^{32}P) cytidine triphosphate (dCTP) (>3000 Ci/mM, New England Nuclear Research Products, Boston, MA) using the nick-translation kit (NEK-004A) from the same source. The filters were washed to a final stringency of 0.1 × SSC, 0.1% sodium dodecyl sulfate (SDS) (Sigma Chemical Co., St. Louis, MO) at 55°C. Autoradiograms were prepared using Kodak X-Omat AR-5 film and intensifying screens at −70°C. Blots were probed using restriction fragments of full-length cDNA for human IL-1 beta [19] and a full-length cDNA for the complete coding region of Il-1 alpha (P.R. Young, SmithKline Beecham Pharmaceuticals) isolated from an activated human monocyte library using a partial cDNA probe described previously [20]. Human alpha-actin was obtained from L. Kedes (Stanford University, CA [21]).

Administration of Dexamethasone Dexamethasone (Sigma Chemical Co., St. Louis, MO) was administered at doses of either 2 (×3) or 10 (×2) mg/kg. The compound was homogenized in 0.5% tragacanth and the suspension was delivered orally by gavage in a volume (ml) of 1:100 body weight. The compound was administered 24 h and 30 min prior to initiation of UV irradiation. The UV-irradiated controls received tragacanth alone.

RESULTS

Exposure for as little as 30 min of UV irradiation (2.3 J/cm²) resulted in a significant inflammatory response as measured by both ear swelling and the acute-phase reactant, SAP (160 and 390% increase, respectively). Continued exposure for up to 3 h resulted in dose-dependent increases in both responses. At 3 h, the severity of the inflammatory lesion had approximately doubled (Table I).

To establish the temporal relationship between UV irradiation and serum amyloid P component (SAP) response, animals were irradiated for 3 h and blood samples were collected for SAP analysis at various times thereafter. As seen in Fig 1, no significant SAP response was seen at 5 h post-UV irradiation, but at 9 and 27 h, a twofold and fourfold increase in SAP levels was observed.

The time courses for IL-1 production, measured by in vitro bioassay and inflammatory cell infiltration, quantitated by the myeloid

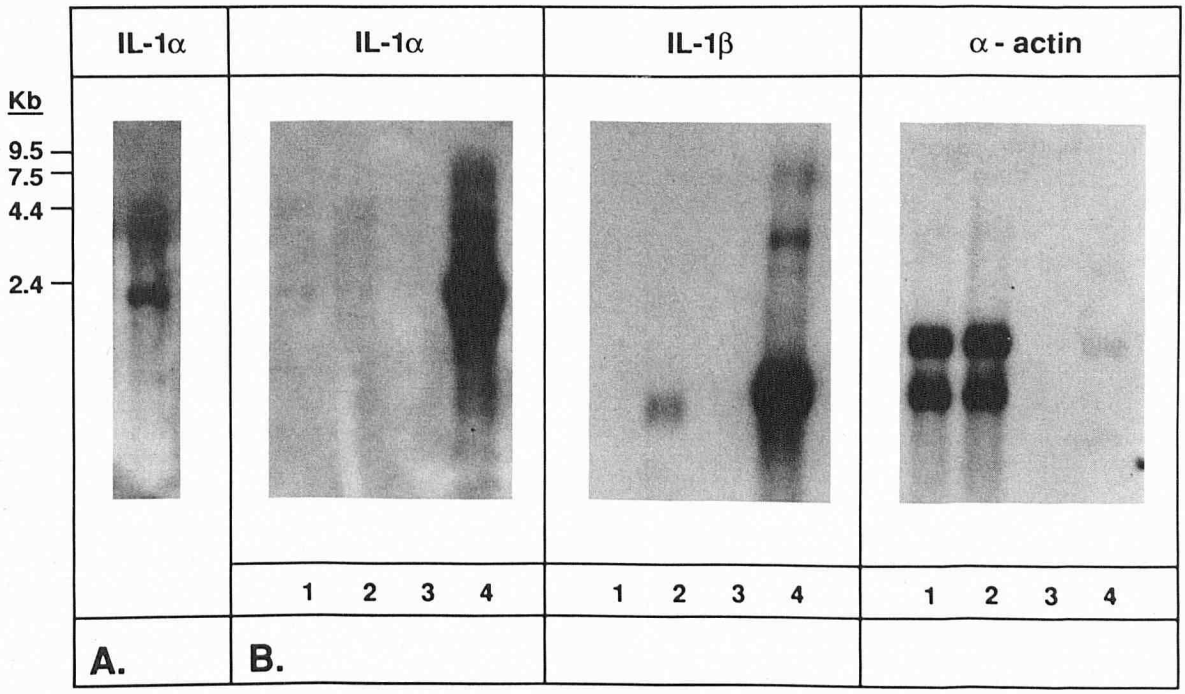

Figure 2. Expression of IL-1 alpha and IL-1 beta in UV-irradiated skin. Northern blots were prepared with: *A*, 10 μg of poly A + RNA from P388D1 cells hybridized with human IL-1 alpha cDNA probe (control for cross-species hybridization); *B*, 5 μg Poly A + RNA from non-irradiated skin, *(lane 1)* 5 μg Poly A + RNA from 3-h irradiated skin UV, harvested 24 h post-irradiation *(lane 2)*; no RNA *(lane 3)*; 2 μg total RNA from human monocytes treated with LPS (as a control for the hybridizations) *(lane 4)*. The blots were hybridized with ^{32}P-dCTP labeled cDNA as indicated in *Materials and Methods.*

cell enzyme marker, myeloperoxidase (MPO) are illustrated in Fig 1. An increase in IL-1 activity preceded the MPO response because a significant increase in IL-1 activity was demonstrable from biopsies taken as early 4 h post-irradiation, whereas, significant increases in MPO activity were observed in tissue excised 7–24 h post-UV.

Northern blot analysis, revealed an increased level of expression of IL-1 beta mRNA in UV-irradiated skin compared to controls. In contrast, the expression of IL-1 alpha mRNA was not affected by UV irradiation (Fig 2). Examination of the time course of IL-1 gene expression clearly showed the temporally related increase in expression of IL-1 beta mRNA during UV irradiation (Fig 3). No enhancement of IL-1 alpha mRNA was detected.

Tables II and III show the relationship between IL-1 and the subsequent inflammatory response, which is further strengthened by the observation that edema (30%), inflammatory cell infiltration (as shown by MPO, 77%), IL-1 production (74%), and SAP response (72%) are all significantly reduced by the administration of the corticosteroid anti-inflammatory agent, dexamethasone.

DISCUSSION

The proinflammatory consequences of UV irradiation of skin have been measured by local changes in vascular beds, permeability changes, and the production of vasoactive mediators, including mast cell amines and arachidonic acid metabolites [22–24]. Although these changes are consistent with the increase in vascular permeability and the acute inflammation observed, they do not explain the systemic sequelae of UV irradiation that include leukocytosis and acute phase reactant response. However, the systemic sequelae are consistant with the response to systemic administration of IL-1, which includes the generation of SAP and leukocytosis [5]. Thus, IL-1 is a candidate as a major mediator of the pathophysiologic changes associated with UV irradiation. Previous studies have suggested that IL-1 is produced by cells both in culture and in vivo following exposure to UV irradiation [6–9,25]. The current study demonstrates that UV irradiation induces the expression of the gene encoding for IL-1 beta.

Although the EL4/IL-2 bioassay has been extensively characterized [13] and shown to be unresponsive to IL-2, IL-3, IL-6 and tumor nerosis factor (TNF), and IL-8, the IL-1 activity in mouse skin was confirmed to be IL-1 using a radioreceptor binding assay that is specific for IL-1. Considerable agreement was seen between the two assays (data not shown).

The mRNA data further demonstrate that the enhanced IL-1 levels are the result of gene expression and de novo synthesis and not related to pre-formed molecules. Currently, little is known about the mechanisms of regulation of IL-1 alpha and IL-1 beta gene transcription or translation, or even why there are two distinct, independently regulated genes. There is little evidence to suggest any significant differences on the spectrum of activity of the two gene products. Isolated human keratinocytes appear to secrete only IL-1 alpha despite the presence of mRNA for both forms. It is possible that in these cells, precursor processing occurs with only IL-1 alpha [26]. It is unknown whether mouse skin can synthesize both precursor forms, but the marked induction of IL-1 activity coupled with an induction of IL-1 beta mRNA strongly suggests that IL-1 beta is the predominate form produced following UV-induced inflammation.

The recent observation of activated (Ha-ras) oncogene in human skin cancers occurring on sun-exposed body sites suggests that UV irradiation may be associated with activation of a variety of genes [27]. That one of the early events in the pathophysiologic process may be an induction of genes for cytokine production is shown by the present study; however, it is not known whether the level of exposure delivered in the current study is sufficient to activate oncogenes or whether that event is associated with chronic exposure and subsequent carcinogenesis as has been shown by other studies [28]. The relationship between the inflammatory response, tissue repair, and subsequent development of a tumor may be more than just coincidental as suggested by studies using Sencar mice. These mice develop skin tumors with a single exposure to UV irradiation and show exaggerated inflammatory and repair responses [29]. It is possible to speculate that the enhanced inflammatory response is perhaps mediated at least in part by IL-1. Recent studies have suggested that IL-1 may play a role as a tumor growth factor [30], thus further implicating this cytokine in tumorigenesis. In addition, the immunosuppressive effects of UV irradiation have been attributed

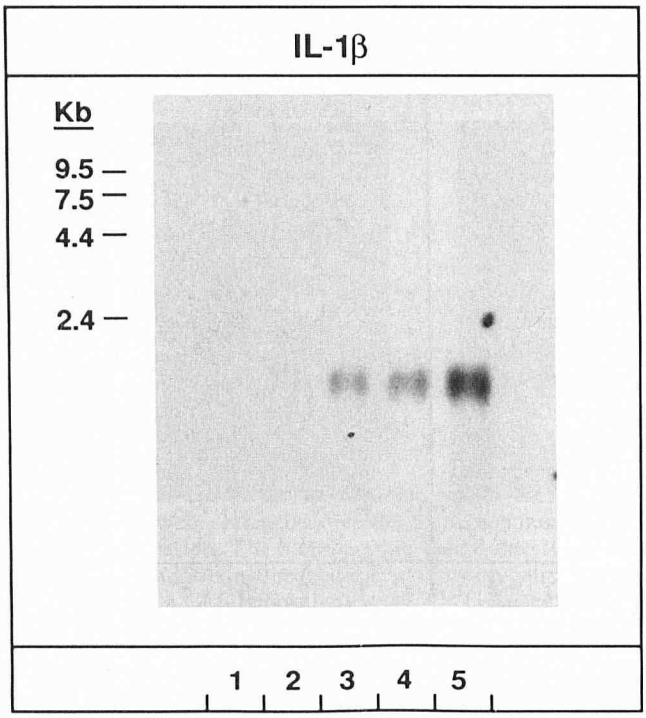

Figure 3. Time course of IL-1 beta expression following UV irradiation. The Northern blot was prepared with 5 μg Poly A + RNA as follows: non-irradiated control *(lane 1);* (2-5), 3-h UV irradiation then harvested: immediately *(lane 2),* 3 h post-UV *(lane 3),* 9 h post-UV *(lane 4),* 21 h post-UV *(lane 5).* The blot was hybridized with ^{32}P-dCTP labeled cDNA probes for IL-1 beta as indicated in *Materials and Methods.*

to altered antigen presentation and suppressor cell induction [31,32]. However, the role of IL-1 in supporting suppressor cell generation and proliferation in UV-irradiated mice should be reinvestigated when specific inhibitors or receptor antagonists become available. These events, in consort with activation of oncogenes, may facilitate the outgrowth of tumors [33]. With the growing concern about the pathologic consequences of increased exposure to UV irradiation, it becomes important to understand the molecular mechanisms involved in this process and to provide the means pharmacologically to intervene in the process. The results with the corticosteroid anti-inflammatory agent, dexamethasone, demonstrate that it is possible to alter the cascade pharmacologically and help to strengthen further the speculation that IL-1 is an important participant in that cascade. It is hoped that further studies will elucidate some of the relationships between the events described and suggest other means to manipulate the systemic consequences of exposure to UV irradiation.

Table II. Effect of Dexamethasone on the Inflammatory Response to UV Irradiation[a]

Treatment	Number	Edema ($\times 10^{-3}$ cm)	MPO (units/ear)
UV vehicle control	6	47.7 ± 0.4	0.22 ± 0.02
Dexamethasone (10 mg/kg × 2)	6	33.2 ± 1.5[b]	0.05 ± 0.005[b]

[a] Balb/c mice were administered drug orally − 24 hr and 30 min prior to initiation of 3-h UV irradiation. Edema was read 24 h later and tissue was sampled for MPO analysis. Data shown are mean ± SEM.
[b] Statistically significant at $p < 0.001$.

Table III. Effect of Dexamethasone on UV-Induced Production of IL-1 and SAP[a]

Treatment	n	IL-1 (units/ml)	n	SAP (μg/ml)
No UV	6	76.6 ± 9.4	5	23.5 ± 5.3
UV + vehicle	6	118.9 ± 14.2	5	124.3 ± 21.9
UV + dexamethasone (2 mg/kg × 2)	6	87.5 ± 24.5[b]	6	44.3 ± 7.5[c]

[a] Balb/c mice were given either nothing, vehicle, or dexamethasone and exposed to 3 h of UV irradiation. Biopsies were taken 24 h later and cultured as described. Culture fluids were assayed for IL-1 activity. Serum was harvested at 24 h and assayed for SAP concentration.
[b] Statistically significant at a $p < 0.05$.
[c] Statistically significant at a $p < 0.001$.

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